REMARKS/ARGUMENTS

Claims 23-37 are active. New claims 23-37 find support in the original claims and specification as follows: claims 23-24 (claims 1 and 4, page 14). Claim 24 corresponds to the elected species. Claim 25-28 (claims 5-8), claim 29 (claim 14), claim 30 (claim 4), claim 31 (claim 19) claim 32 (claim 10, page 37, claim 33 (claim 19), claim 34 (claim 15), claim 35 (claim 20), claim 36 (claim 3) and claim 37 (page 18, last paragraph).

To more easily identify the locations of the claimed polymorphisms in the IRS-2 gene sequence, the Sequence Listing has been revised to include the 143,409 bp sequence identified by AL162497 which is disclosed on page 44, last paragraph, of the specification. Since AL162497 is an antisense sequence, its reverse complement (i.e., its complement in 5' to 3' orientation) has been added to the Sequence Listing as SEQ ID NO: 19. Polymorphisms (a) through (f) are now identified by references to particular polynucleotides in SEQ ID NO: 19. The AL162497 is a polymorphic human IRS-2 sequence which does not contain polymorphisms (a) and (b), but which contains polymorphisms (c)-(f). However, the positions of polymorphisms (a) and (b) are clearly identifiable from this sequence.

Polymorphism (a) C-4587A occurs at position 12,936 of SEQ ID NO: 19. At this position the polymorphic variant would have an "A" instead of the "C" as described in the middle of page 14 of the specification.

Polymorphism (b) AT-2510-del corresponds to deletion of "AT" at positions 15,012-15,013 of SEQ ID NO: 19.

Polymorphism (c), A164C, appears in the polymorphic variant of SEQ ID NO: 19 where position 16,359 is "C" instead of the wild-type "A".

Polymorphism (d), A15870G, appears in the polymorphic variant of SEQ ID NO: 19 where position 33,392 is "G" instead of the wild-type "A".

Polymorphism (e), A29793G, appears in the polymorphic variant of SEQ ID NO: 19 where position 47,315 is "G" instead of the wild-type "A".

Polymorphism (f), C31532 del, appears in the polymorphic variant of SEQ ID NO: 19 as a deletion of a "C" nucleotide which would otherwise appear between the two "A" nucleotides at positions 49,053-49,054 in the wild-type.

The translation initiation codon "ATG" appears at positions 17,523-17,525 of SEQ ID NO: 19. Correspondence of the relative nucleotide positions of SEQ ID NO: 19 and the positions disclosed relative to the start codon in the specification may be easily deduced. For example, polymorphism (a) is disclosed on page 14 of the specification as being "at position 4,587 upstream of the translation initiation codon". Subtracting 4,587 from 17,523 (the translation initiation codon position in SEQ ID NO: 19) provides the difference of 12,936 which is the relative position of polymorphism (a) in SEQ ID NO: 19.

Accordingly, the Applicants do not believe that any new matter has been introduced. Favorable consideration of this amendment and allowance of this application are now respectfully requested.

Sequence Listing Statement

As required by 37 C.F.R. 1.821(f), the sequence information recorded in the computer-readable form (CRF) of the substitute Sequence Listing is identical to that in the paper copy of the substitute Sequence Listing; or if this substitute Sequence Listing is electronically-filed, then the sequences in the electronically filed Sequence Listing are identical to the sequences disclosed in this application. Pursuant to 37 C.F.R. 1.821(g) the Applicants state that no new matter has been introduced. CHECKER indicates "no errors".

Restriction/Election

The Applicants previously elected with traverse **Group I**, claims 1-8, 14, 15 and 19-22, directed to a method for assessing risk of drug-induced granulocytopenia, and the **species genetic polymorphism (e) (A29793G)**. The requirement has been made FINAL. The Applicants understand that additional species will be rejoined and examined upon an indication of allowability for a generic claim reading on the elected species. The Applicants respectfully request that the claims of the nonelected group(s) which depend from or otherwise include all the limitations of an allowed elected claim, be rejoined upon an indication of allowability for the elected claim, see MPEP 821.04.

Objection

Claims 5-8 were objected to as being improper multiple dependent claims. This issue is now moot since these claims have been cancelled.

Rejection—35 U.S.C. §112, first paragraph

Claims 1-4, 14, 15, and 19-22 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description. This rejection is moot in view of the cancellation of these claims. The Applicants do not believe that this rejection would apply to the new claims in which the location of each polymorphism is clearly identified by reference to the IRS-2 gene sequence in SEQ ID NO: 19.

Rejection—35 U.S.C. §112, first paragraph

Claims 1-4, 14, 15, and 19-22 were rejected under 35 U.S.C. 112, first paragraph, as lacking adequate enablement. This rejection is moot in view of the cancellation of these claims. It is believed that this rejection would not apply to the new claims, because the specification clearly identifies a representative number of polymorphisms associated with development of granulocytopenia induced by administration of a specific drug—vesnarinone. Moreover, as described in Example 1 (specification, page 39, *ff.*), a large cohort of subjects (13 + 17 + 33 + 21 = 84, specification page 41, lines 8-13) who had received vesnarinone were divided into two groups—those with granulocytopenia and those without (specification, page 40, last paragraph). These results indicated that out of 188 SNP (single nucleotide polymorphisms) in 115 different genes, that the most statistically significant correlation between granulocytopenia was located in the IRS-2 gene (page 43).

The inventors conducted further association analysis of the human IRS-2 gene as shown in Example 2 (page 44, *ff.*) which "revealed that six polymorphisms were intimately associated with granulocytopenia induced by vesnarinone (specification, bottom of page 46). Tables 1-6 beginning on page 47 of the specification detail the statistical analysis of these polymorphisms of the human IRS-2 gene. Based on these results, there is no basis for asserting that one with skill in the art would not be able to make or use the invention, especially with respect to granulocytopenia associated with vesnarinone administration as required by claims 29, 31, 33 and 35.

With respect to the scope of enablement issue with respect to whether these polymorphisms correlate with granulocytopenia associated with drugs other than vesnarinone, the Applicants note that once an association between polymorphisms of the IRS-2 gene and drug-induced granulocytopenia is identified, that only routine experimentation would be required to determine whether granulocytopenia caused by other

drugs associates with IRS-2 polymorphisms. Even a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed, *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Based on the application of the factors described by Wands, no undue experimentation would be required to practice the present invention:

(A) the breadth of the present claims limits the method to associations between a particular disorder, granulocytopenia, and to associations between polymorphisms of the IRS-2 gene and this disorder. There are a limited number of drugs that cause granulocytopenia such are well-known to those of skill in the art.

(B) The nature of the invention involves association of polymorphisms in the IRS-2 gene with granulocytopenia.

(C) The state of the prior art shows that methods of associating various disease, disorders, and predispositions with genetic polymorphisms were well-known.

(D) The level of ordinary skill in the medical and molecular biological arts is high, generally M.D., Ph.D or post-doctoral level.

(E) The level of predictability in the art is high, since methods for detecting genetic polymorphisms are well-known and the inventors have specifically identified a human gene associated with granulocytopenia. Moreover, the page 51 of the specification discloses that the IRS-2 gene is closely associated with granulocytic differentiation, which in combination with the results obtained by the inventors for vesnarinone, suggest that polymorphisms of this gene would be important in other drug-induced granulocytopenias.

(F) and (G) The amount of direction provided by the present inventors is high and the claimed method is exemplified in a large cohort of 84 subjects, not merely in a single isolated

human subject. The same methods exemplified in the specification may be simply applied to subjects experience drug-induced granulocytopenia associated with other drugs.

(H) The quantity of experimentation needed to make or use the invention is limited to merely determining whether other subjects who experience drug-induced granulocytopenia have polymorphisms in their IRS-2 genes which correlate with their disorder. It does not requiring attempting to identify whether drug-induced granulocytopenia associates with genes other than IRS-2 (such as those conditions mentioned by the Examiner on page 7 of the Official Action), nor does it require association of disorders other than granulocytopenia with the IRS-2 gene. Accordingly, the Applicants respectfully submit that this rejection would not apply to the present claims.

Conclusion

In view of the amendments and remarks above, the Applicants respectfully submit that this application is now in condition for allowance. An early notice to that effect is earnestly solicited.

Respectfully submitted,

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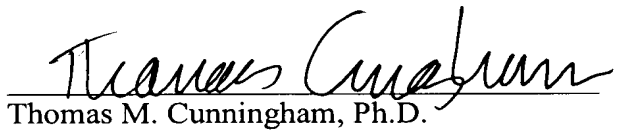

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